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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,575	EIBL, JOHANN	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may ba available under the provisions of 37 CFR 1.136(a). In no avent, howaver, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If tha period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expira SIX (6) MONTHS from tha mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statuta, causa tha application to becoma ABANDONED (35 U.S.C. § 133). Any reply received by tha Office later than three months after the mailing data of this communication, even if timely filed, may reduca any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-104* is/are pending in the application.

4a) Of the above claim(s) *3-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 99-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Susan Hanley is now the examiner for this application. Her contact information appears at the conclusion of this Office action.

Applicants amendment and arguments filed 1/21/05 are acknowledged.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-104 and the species (A) structural proteins, and (B) allogenic collagen as the structural protein in the reply filed on 1/1/04 is acknowledged. Applicant filed additional arguments filed 1/21/05. Since the Office action of 3/12/04 was not made Final, the arguments will be addressed. The traversal is on the ground(s) that the imposition of the species election requirement allows the Examiner to presuppose that claim 1 is not allowable without providing an examination on the merits. Applicant asserts that the Examiner's claim of excessive search burden is not on point because if an independent claim is allowable, there is no need to search the dependent claims. Applicant asserts that the Examiner could have rejected all of the claims that depend from independent claim 1. Applicant then argues that a hypothetical amendment to claim 1 should necessitate an explanation as to why the amendment overcomes that rejection which relieves the burden placed on the Examiner and that the Examiner has procedural recourse to relieve said burden.

This is not found persuasive because Applicant's argument that the specie election precludes an examination of the independent claim is unfounded. In a specie election, the specie and the generic claim are always examined. The instant specie elections are valid because each additional component is an active ingredient that would materially affect the basic and novel characteristics of the claimed invention. Thus, it is proper to consider that searching each and every one of the added active ingredients requires a separate search inasmuch as the different active ingredients are not classified together or recognized in the art as being co-extensive. Responding to Applicant's argument that there is no need to search the dependent claims if the independent claim is allowable, all limitations must be searched because each

limitation changes the scope of the invention. Furthermore, issues under 35 U.S.C. 112 must be considered. Responding to Applicant's argument a hypothetical amendment, this is a purely speculative argument.

Claims 3-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/2/04.

The requirement is still deemed proper and is therefore made FINAL.

Response to Arguments

Applicant's arguments with respect to claims 1, 2 and 99-104 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

Claim 102 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 102 is rejected because it is unclear if a carrier material is subjected to viral decontamination and then combined with the active agents or if "one or more of the active agents" are applied to a carrier material and the resulting composition comprising the active agents and the carrier are subjected to viral decontamination.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2 and 99-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacPhee et al. (US 6,054,122) in view of Burnouf (Colloque lNSERM (1989) 175: 373-81) and Racanelli et al. (US 5,254,536).

MacPhee et al. disclose fibrin sealant compositions comprising purified, lyophilized fibrinogen, plasminogen, Factor XIII (transglutaminase) that are of human origin and which are virally inactivated (col. 9, lines 57-68). The teaching of blood products of human origin meets the limitation of allogenic sources, as in instant claim 1. The disclosure of fibrinogen, thrombin and transglutaminase meets the instantly claimed active agents of claim 1 (i)-(iii). MacPhee et al. emphasize the need to purify and pathogen-inactivate, as in instant claim 2, all components of the composition (col. 26, lines 9-20). MacPhee et al. further teach that it is desirable to add compounds that inhibit the breakdown of the fibrin clot (col. 26, lines 30-35).

MacPhee et al. disclose a fibrin sealant bandage wherein dry, virally inactive agents are disposed in layers on a backing (col. 2 to col. 28, bridging). The various active agents can be formulated with a scaffold comprising human proteins in order to minimize immunogenicity problems (col. 13, lines 17-25). Such a protein can be collagen (col. 29, lines 25-35), which meets the limitations of instant claim 99 that requires all of the active substances on an allogenic provision extracellular matrix. The dry bandage can also contain anhydrous $CaCl_2$ to keep the active components dry (col. 28, lines 51-59), as required by instant claim 103.

MacPhee et al. disclose that the components for fibrin sealants are also traditionally disposed in separate containers: (1) fibrinogen concentrate witch contains fibronectin, Factor XIII and von Willebrand factor; (2) dried human or bovine thrombin; and (3) calcium ions. The components are mixed together at the time of use and applied to a tissue (col. 4, lines 7-21). This disclosure meets instant claims 100 and 101 which are related to the separate disposition of the active substances in separate containers.

MacPhee et al. do not teach that the composition comprises a serpin that does not inhibit elastase or collagenase (as in instant claims 1) or that said serpin is sterilized separately from the other agents (as in instant claim 1).

Burnouf discloses separate methods of inactivating viral contamination in human plasma protein fractions. Burnouf states that not all treatments are efficacious for inactivating all pathogenic human blood-borne viruses and the purification procedure influence the virus elimination step (p. 373, first paragraph). The disclosure of human blood source meets the requirement that the active agents are allogenic, as in instant claim 1. Burnouf discloses separate methods of purifying and virally decontaminating fibrinogen, prothrombin complex, alpha 1-antitrypsin and factor IX (p. 377-338). Each plasma protein requires significantly different steps to successfully deplete viral contamination. For example, fibrinogen is inactivation at >24 degrees C for 6 hours in tri-(n-butyl) phosphate and 1% tween-80 and then precipitated. alpha 1-antitrypsin is ultrafiltered, chromatographed on a DEAE exchanger, size-exclusion chromatography and then pasteurized.

Racanelli et al. disclose a topical pharmaceutical composition for controlling localized bleeding. The composition comprises PAI-1, a serpin that counteracts excessive fibrinolysis (col. 1, lies 61-63), fibrinogen, thrombin and microfibrillar collagen (col. 7, lines 27-30). Preferably the PAI-1 is recombinant. Racanelli et al. also teach that the components can be packed in separate, sterile containers that can be reconstituted at the time of use (col. 7, lines 40-45).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a topical medicament to stop bleeding composition by augmenting the active agents taught by MacPhee et al. with a serpin that does not inhibit elastase or collagenase such as PAI-1 and that said PAI-1 is sterilized separately from the other agents. The ordinary artisan would have been motivated to add PAI-1 to the composition taught by MacPhee et al. because MacPhee et al. expressly disclosed the desirability of adding a fibrinolytic agent to their composition. The fibrinolytic agent disclosed by Racanelli et al., recombinant PAI-1, counteracts excessive fibrinolysis, thus meeting the express need of

MacPhee et al. The ordinary artisan would have had a reasonable expectation that PAI-1 would successfully work in the composition of MacPhee et al. because Racanelli et al. teach that the combination of PAI-1, fibrinogen, thrombin and collagen makes an effective tissue sealant.

The ordinary artisan would have been motivated to sterilize the PAI-1 separately from the other active agents and to package said agents separately because Burnouf teaches that the isolation and viral inactivation methods for each of the claimed components from a human blood source should be done separately because each active substance has different requirements for purification and viral inactivation. The ordinary artisan would have had a reasonable expectation that PAI-1 could be successfully isolated and virally inactivated separate from the other active agents because Burnouf teaches how to accomplish this.

The ordinary artisan would have been motivated to add PAI-1 to a separate vial to inhibit fibrinolysis or to a fibrin sealant bandage, both of which are disclosed by MacPhee et al., because PAI-1 is an agent that will prevent fibrinolysis of a clot, which MacPhee et al. stated was a desirable property of their layered scaffold (bandage). Further, Racanelli et al. also teach the combination of PAI-1, fibrinogen, thrombin and collagen makes an effective tissue sealant. The ordinary artisan would have had a reasonable expectation that a bandage comprising allogenic PAI-1, fibrinogen, thrombin and collagen would serve as a topical medicament to stop bleeding because fibrinogen, thrombin and transglutaminase are known to accomplish this when they are present together in a bandage or applied together from reconstituted concentrates. PAI-1 would be expected to prevent fibrinolysis because Racanelli et al. demonstrated this property.

Claims 1, 2 and 99-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacPhee et al. (US 6,054,122) in view of Burnouf (Colloque INSERM (1989) 175: 373-81) and Racanelli et al. (US 5,254,536) as applied to claims 1, 2 and 99-103 above, and further in view of Stroetmann (US 4,442,655) which was cited in the IDS of 11/16/01.

The disclosure by MacPhee et al. is discussed *supra*. MacPhee et al. teach a fibrin sealant bandage containing a drying agent such as anhydrous $CaCl_2$.

MacPhee et al. do not teach the solidification of fibrin in an allogenic matrix by contacting said matrix with a combination comprising a dehydrating agent and an allogenic transglutaminase.

Stroetmann et al. disclose that it is advantageous to add a dehydrating agent to a solution containing fibrinogen and thrombin for the purpose of making a dry preparation of a fibrin sealant. The dehydrating agent will cause the loss water from said solution and the product will be denser and have a greater mechanical strength (col. 3, lines 50-55 and col. 4, lines 15-20). Stroetmann et al. also teach that the resulting dry preparation can be further strengthened by crosslinking it with factor XIII (col. 9, lines 50-68). Stroetmann et al. also teach that it is desirable to add a fibrinolysis inhibitor such as a PAI to the dry preparation (col. 6, lines 65-68). Stroetmann et al. also teach that the dry preparation should be sterilized (col. 11, lines 5-10).

It would have been obvious to one or ordinary skill at the time the invention was made to stabilize the modified tissue sealant taught by MacPhee et al., Burnof and Racanelli et al., comprising fibrin, thrombin, PAI-1 and transglutaminase on a collagen matrix, by adding the combination of a dehydrating agent and transglutaminase during the process of making. The ordinary artisan would have been motivated to do so because such treatment makes dry preparation having greater mechanical strength. The ordinary artisan would have had a reasonable expectation that the modified tissue sealant taught by MacPhee et al., Burnof and Racanelli et al. could be successfully treated in the manner taught by Stroetmann et al. because said modified tissue sealant and the dry preparation of Stroetmann et al. are composed of the same allogenic, virally depleted elements: fibrinogen, thrombin, factor XIII, collagen and PAI. Thus the ordinary artisan would have reasonably expected that the modified tissue sealant of MacPhee et al., Burnof and Racanelli et al. would react with a dehydrating agent and factor XIII in the same manner to produce a denser, cross-linked dry fibrin sealant preparation (col. 9, lines 50-68).

Claims 1, 2 and 99-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stroetmann (US 4,442,655), which was cited in the IDS of 11/16/01, in view of MacPhee et al. (US 6,054,122), Burnouf (Colloque INSERM (1989) 175: 373-81) and Racanelli et al. (US 5,254,536).

Stroetmann et al. disclose a dry preparation comprising a fibrin sealant, wherein an aqueous solution comprising fibrinogen and salts is combined with a drying agent such as ethylene glycol. The fibrinogen can be isolated and lyophilized (col. 3, lines 50-55 and col. 4, lines 15-20). This dry preparation can be enriched with collagen, thrombin and fibrinolysis inhibitors (col. 6, lines 21-68). It is also desirable to crosslink the dry preparation with factor XIII to increase its mechanical strength. Stroetmann et al. also teach that the dry preparation should be sterilized (col. 11, lines 5-10).

Stroetmann et al. do not teach that all of the active agents are from an allogenic source (claims 2 and 104), the composition comprises a serpin that does not inhibit elastase or collagenase (as in instant claims 1, 100-102) or that said serpin is sterilized separately from the other agents (as in instant claim 1).

The disclosures by MacPhee et al., Burnouf and Racanelli et al. are discussed *supra.*

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the dry preparation taught by Stroetmann et al. by using he active agents from an allogenic source and adding a serpin that does not inhibit elastase or collagenase, wherein said serpin is sterilized separately from the other agents. The ordinary artisan would have been motivated to add PAI-1 to the composition taught by Stroetmann et al. because Stroetmann et al. expressly disclosed the desirability of adding a fibrinolytic agent to their composition to prevent premature clot degradation. The fibrinolytic agent disclosed by Racanelli et al., recombinant PAI-1, counteracts excessive fibrinolysis, thus meeting the express need of Stroetmann et al. The ordinary artisan would have had a reasonable expectation that PAI-1 would successfully work in the composition of Stroetmann et al. because Racanelli et al. teach that the combination of PAI-1, fibrinogen, thrombin and collagen makes an effective tissue sealant.

The ordinary artisan would have been motivated to sterilize the PAI-1 separately from the other active agents and to package said agents separately because Burnouf teaches that the isolation and viral inactivation methods for each of the claimed components from a human blood source should be done separately because each active substance has different requirements for purification and viral inactivation. The ordinary artisan would have had a reasonable expectation that PAI-1 could be successfully isolated and virally inactivated separate from the other active agents because Burnouf teaches how to accomplish this.

The ordinary artisan would have been motivated to make the dry preparation taught by Stroetmann et al. from allogenic sources because MacPhee et al. disclose that the use of an allogenic source reduces adverse immune reaction to the preparation. The ordinary artisan would have had a reasonable expectation that the dry preparation taught by Stroetmann et al. could be made from allogenic sources because MacPhee et al. and Burnouf teach the isolation of the various active agents from human blood.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).